PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P031450WO/CJM	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/03407	International filing date *(day/month/year)* 06.08.2003	Priority date *(day/month/year)* 07.08.2002
International Patent Classification (IPC) or both national classification and IPC C12N5/06		
Applicant NOVATHERA LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08.03.2004	22.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Teyssier, B Telephone No. +31 70 340-2062

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/03407

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-18 as originally filed

Claims, Numbers

1-21 as originally filed

Drawings, Sheets

1-4 as originally filed

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12 (IA)

   because:

   ☒ the said international application, or the said claims Nos. 12 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6, 12-14
	No:	Claims	7-11, 17, 20, 21
Inventive step (IS)	Yes:	Claims	1-6
	No:	Claims	7-21
Industrial applicability (IA)	Yes:	Claims	1-11, 13-21
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 12 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35 with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1 Corti *et al.*, *American Journal of Respiratory Cell & Molecular Biology* 1996, 14(4), 309-315

D2 Shannon J M *et al.*, *Development* 1999, 126(8), 1675-1688 (April 1999)

D3 Gonzales L W *et al.*, *American Journal of Physiology. Lung Cellular & Molecular Physiology* 2002, 283(5), L940-L951 (November 2002, **prepublished 17-06-2002**)

D4 WO 01/42425 A (Childrens Hospital Los Angeles Research Institute) 14 June 2001

D5 Fehrenbach H, *Respiratory Research* 2001, 2(1), 33-46

Example 2 of D4 teaches that foetal type 2 alveolar epithelial cells (AE2) express telomerase and that telomerase expression is reinduced in adult AE2 cells following lung injury; the possible effects of such a reinduction of telomerase expression on the length of telomeres in adult cells is not described. However, the possible reinduction of telomerase expression described in D4 makes it unclear whether a reference level of telomerase expression or telomere length in lung cells can be defined. It is also observed that the relative term "longer" has no precisely defined meaning and thus render the definition of the subject-matter of claim 10 unclear. Consequentely, the length of telomeres cannot be taken into account when assessing the novelty of the subject-matter of claim 10.

D1 teaches the isolation and culture of murine AE2; the cells are obtained with a purity of 95.0% ± 6.2; in view of this result the obtention of AE2 in high purity, possibly up to 100%, appears within reach for the skilled person. D2 teaches the induction of AE2 differentiation in rat embryonic tracheal epithelium in culture. D3, which belongs to the state of the art due to its prepublication on 17 June 2002, teaches the differentiation of human foetal lung epithelium into AE2 in culture; according to D3, dexamethasone, a glucocorticoid, is necessary for AE2 differentiation.

Since AE2 are SPC+ cells, in view of the prior art described in D1, D2 and D3, the subject-matter of claims 7-11 and 17 is not new (Article 33(2) PCT) and the additionnal subject-matter of claims

15, 16, 18 and 19 does not involve an inventive step (Article 33(3) PCT). No difference can be acknowledged based on purity, cell density or size of the culture or on *in vitro* differentiation from embryonic stem cells (ES).

The subject-matter of claim 20 is not new over D2 and D3 and the subject-matter of claim 21 is not new over the prior art cited in the introduction of D2 (Shannon 1994-1998).

The subject-matter of claims 1-6 is new and inventive because none of the prior art documents describe AE2 differentiation from ES, or other types of pluripotent cells which can give rise to embryoid bodies in suspension culture (Article 33(2,3) PCT).

D4 suggests medical applications of lung stem cells (see the claims), but not of purified AE2 cells. None of the documents D1-D3 and D5 mentions potential medical applications of AE2. In view of the lack of references to specific medical applications of AE2 in the prior art, the subject-matter of claims 12-14 appears to be meet the requirements of Article 33(2) PCT, but not those of Articles 5, 6 and 33(3) PCT: In the absence of precise and specific examples as to therapeutic uses of AE2 cells in the application as well as in the prior art, the merely formal support provided by pages 6 and 7 of the description does not allow the skilled person to carry out AE2 cell therapy, thus the subject-matter of claims 12-14 lacks support and disclosure in the application (Articles 5, 6 PCT), and it is not apparent which technical problem is solved by the alleged invention, i.e. which actual pathological condition or disease is to be treated, and whether the problem is actually solved in that the treatment is clinically effective or, at least, that reasonable expectations of clinical sucess exist based on *ex vivo* data (Article 33(3) PCT).

For the assessment of the present claims 12-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.